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L4: Entry 25 of 31 File: USPT Mar 7, 1995

DOCUMENT-IDENTIFIER: US 5395825 A
TITLE: Fertility regulation with transforming growth factor .beta.

BSPR:
The invention further provides methods of increasing the success rate of assisted reproduction comprising administering transforming growth factor .beta. to ovum, sperm or conceptus prior to, simultaneously with, or following introduction of ovum, sperm or conceptus into the reproductive tract of a female mammal. Applicants have discovered that during normal mammalian pregnancy, trophoblast fibronectin, localized in the placental-uterine junction, is important to implantation. Thus, TGF.beta., which has been found to (1) concominantly stimulate the production of trophoblast fibronectin; and (2) promote adhesiveness of trophoblast to the extracellular matrix, effectively enhances the implantation of the ovum or conceptus.

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L4: Entry 19 of 31 File: USPT Dec 2, 1997

DOCUMENT-IDENTIFIER: US 5693479 A
TITLE: Fertility determination with transforming growth factor .beta.

BSPR:
The invention further provides methods of increasing the success rate of assisted reproduction comprising administering transforming growth factor .beta. to ovum, sperm or conceptus prior to, simultaneously with, or following introduction of ovum, sperm or conceptus into the reproductive tract of a female mammal. Applicants have discovered that during normal mammalian pregnancy, trophoblast fibronectin, localized in the placental-uterine junction, is important to implantation. Thus, TGF.beta., which has been found to (1) concominantly stimulate the production of trophoblast fibronectin; and (2) promote adhesiveness of trophoblast to the extracellular matrix, effectively enhances the implantation of the ovum or conceptus.

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Related Articles | External Links

TITLE: Cytokine-leukocyte networks and the establishment of pregnancy.

AUTHORS: Robertson SA; Mau VJ; Hudson SN; Tremellen KP

AUTHOR AFFILIATION: Department of Obstetrics and Gynaecology, The University of Adelaide, South Australia.

SOURCE: Am J Reprod Immunol 1997 Jun;37(6):438-42

CITATION IDS: PMID: 9228299 UI: 97372035

ABSTRACT: PROBLEM: Factors in seminal plasma stimulate an intense but transient inflammatory response in the murine endometrium at mating. The aim of our current studies is to delineate the cytokine-leukocyte interactions comprising this response and to elucidate the significance of these events in changes in the maternal immune system and as determinants of pregnancy outcome. METHOD: We have reviewed our recent findings. RESULTS: Transforming growth factor (TGF)-beta1 has been identified as the inflammation-inducing moiety in seminal plasma. Seminal TGFbeta1 initiates endometrial leukocyte infiltration by up-regulating epithelial cell expression of granulocyte-macrophage colony-stimulating factor. Other cytokines and chemokines including regulated and normal T-cell expressed and secreted (RANTES), macrophage inflammatory protein (MIP)-1alpha, MIP-1beta, and monocyte chemotactic protein-1 are also implicated as mediators of macrophage and granulocyte recruitment and activation. One consequence of this inflammatory response is the induction of a transient state of hyporesponsiveness to paternal major histocompatibility class I antigens. CONCLUSION: Our studies suggest that semen may play a critical role in providing the antigenic and environmental signals necessary to initiate an appropriate maternal immune response to the conceptus during pregnancy.

MAIN MESH HEADINGS: Cytokines/*physiology
Leukocytes/*physiology
Pregnancy/*immunology

ADDITIONAL MESH Animal

HEADINGS:	**Chemotaxis, Leukocyte** **Endometrium/cytology** **Endometrium/metabolism** **Epithelium/cytology** **Epithelium/metabolism** **Female** **Human** **HLA Antigens/immunology** **Inflammation** **Isoantigens/immunology** **Male** **Mice** **Mice, Inbred Strains** **Models, Immunological** **Semen/immunology** **Semen/physiology** **Support, Non-U.S. Gov't** **1997/06** **1997/01 00:00**
PUBLICATION TYPES:	**JOURNAL ARTICLE** **REVIEW** **REVIEW, TUTORIAL**
CAS REGISTRY NUMBERS:	**0 (Cytokines)** **0 (HLA Antigens)** **0 (Isoantigens)**
LANGUAGES:	**Eng**

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Related Articles

TITLE: Interactions between the immune system and the ruminant conceptus.

AUTHORS: Hansen PJ

AUTHOR AFFILIATION: Department of Dairy and Poultry Sciences, University of Florida, Gainesville 32611-0920, USA.

SOURCE: J Reprod Fertil Suppl 1995;49:69-82

CITATION IDS: PMID: 7623350 UI: 95349042

ABSTRACT: Interactions of the conceptus with the immune system can involve either anti-sperm or anti-conceptus immune responses that limit the success of pregnancy of beneficial effects of cytokines released from lymphoid cells on embryonic growth and gene expression. The immune system is functional in the uterus and therefore there is the potential for anti-conceptus immune responses. However, endometrial lymphocytes are distinct in many respects from lymphoid cells at peripheral sites; one major subpopulation expresses the gamma delta T-cell receptor and may not recognize major histocompatibility antigens. There are also several control systems to limit anti-conceptus immune responses. In particular, expression of major histocompatibility antigens on the trophoblast is either absent or of limited distribution. In addition, activation of anti-conceptus immune responses leading to cytolytic responses is further limited by the presence of molecules that can inhibit lymphocyte transformation. The most well-characterized of these are prostaglandin E2 from placental and endometrial tissues, interferon-tau from the trophoblast during early pregnancy, and two endometrial proteins called the uterine milk proteins (UTMP). Progesterone plays a central role in inhibition of immune responses in actions that are mediated at least in part through endometrial secretion of UTMP. Cytokines play important roles as autocrine and paracrine regulators in many tissues including the reproductive tract. In ruminants, the best described example is interferon-tau. Other cytokines found in the reproductive tract or

produced by the conceptus include interleukin-1, leukaemia inhibitory factor, granulocyte-macrophage colony stimulating factor and interleukin-6. It is possible that the major source of cytokines in the reproductive tract is non-lymphoid cells of the endometrium and trophoblast. It is not known to what extent endometrial lymphocytes contribute to the cytokine milieu because no cytokine has been identified as a product of endometrial lymphocytes. However, there is a population of granulated lymphocytes that increase in number and granularity in the luminal epithelium of the late-pregnant ewe that is a potential source of cytokines.

MAIN MESH HEADINGS:
Cattle/*immunology
Pregnancy, Animal/*immunology
Sheep/*immunology
Trophoblast/*immunology
Uterus/*immunology

ADDITIONAL MESH HEADINGS:
Animal
Cytokines/immunology
Endometrium/immunology
Female
Human
Lymphocytes/immunology
Pregnancy
Progesterone/physiology
Support, Non-U.S. Gov't
Support, U.S. Gov't, Non-P.H.S.
Support, U.S. Gov't, P.H.S.
1995/01
1995/01 00:00

PUBLICATION TYPES:
JOURNAL ARTICLE
REVIEW
REVIEW, ACADEMIC

CAS REGISTRY NUMBERS:
0 (Cytokines)
57-83-0 (Progesterone)

LANGUAGES:
Eng

GRANT/CONTRACT ID:
HD 20671/HD/NICHD
HD 26421/HD/NICHD

National Library of Medicine: IGM Full Record Screen

Related Articles | External Links

TITLE:	**The role of cytokines in gestation.**
AUTHORS:	**Robertson SA; Seamark RF; Guilbert LJ; Wegmann TG**
AUTHOR AFFILIATION:	**Department of Obstetrics and Gynaecology, University of Adelaide, South Australia.**
SOURCE:	**Crit Rev Immunol 1994;14(3-4):239-92**
CITATION IDS:	**PMID: 7755875 UI: 95275418**
ABSTRACT:	**Lymphohemopoietic cytokines are now recognized to be central participants in the cellular communication events underlying the complex and dynamic remodeling processes required to accommodate the semiallogeneic conceptus during mammalian reproduction. Cytokines are identified to be particular importance in mediating communications between the conceptus and maternal cells, particularly the uterine epithelium and infiltrating leukocytes, both prior to implantation and as the placenta develops. In this review we summarize recent experimental data concerning the synthesis of various cytokines in uterine and conceptus-derived tissues and highlight current hypotheses for their roles in establishing and maintaining successful pregnancy. It is concluded that complex and finely balanced cytokine networks underpin precise regulatory mechanisms controlling the rate and degree of conceptus development and invasion into maternal tissues.**
MAIN MESH HEADINGS:	**Cytokines/*physiology Pregnancy/*immunology**
ADDITIONAL MESH HEADINGS:	**Animal Cytokines/biosynthesis Decidua/immunology Female Fertilization/immunology Gestational Age Human Placenta/immunology Uterus/immunology 1994/01 1994/01 00:00**
PUBLICATION TYPES:	**JOURNAL ARTICLE**

PUBLICATION TYPES: JOURNAL ARTICLE
REVIEW
REVIEW, ACADEMIC

CAS REGISTRY NUMBERS: 0 (Cytokines)

LANGUAGES: Eng

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L6: Entry 4 of 5 File: USPT Sep 9, 1997

DOCUMENT-IDENTIFIER: US 5665556 A
TITLE: Complement components and binding ligands in fertility

DEPR:
This invention is based on the recognition by the inventors that acrosome-reacted sperm bound to a mAb (H316) directed to a trophoblast cell surface antigen, and that the same antigen, present on leucocytes as well, was identical to a C binding protein, gp45-70, also known as the membrane cofactor protein (MCP). The antigen identified by the H316 mAb which is identical to MCP is also the same as the HuLy-m5 antigen (Johnson, P. M. et al., in: Reproductive Immunology 1989, Mettler & Billington (eds.), Elsevier, Amsterdam (in press). Under the current system of nomenclature, this antigen has been designated CD46. As a result of this discovery, the inventors conceived of a role for MCP, as a C binding protein or a C receptor (CR) on the surface of gametes, in the process of sperm-egg interaction during the fertilization process. The invention is therefore directed to the exploitation of the presence of this CR on gametes in the diagnosis of infertility, in the identification and isolation of acrosome-reacted sperm, in the promotion or inhibition of fertilization in vitro or in vivo, and in the treatment of infertility.

DEPR:
The unexpected finding that binding of H316 to the human sperm surface occurs only after acrosomal changes induced by incubation in capacitation media or calcium ionophore treatment may provide a clue for understanding the functional significance of this antigen on sperm, and indicates that the antigen recognized by H316 may also be useful as a clinical marker for sperm capacitation or acrosome reaction. Another mAb described by Wolf et al., Biol. Reprod. 32:1157-62 (1985), recognizes a human acrosomal antigen that appears to be lost with capacitation/acrosome reaction (the reverse of that observed with H316). Expression of the H316 antigen on sperm from men with unexplained infertility, may serve as a diagnostic tool in understanding, as well as in diagnosing, male infertility. Furthermore, antibodies to the antigen recognized by H316 would be expected to inhibit sperm penetration of homologous eggs.

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L8: Entry 4 of 21 File: USPT Sep 28, 1999

DOCUMENT-IDENTIFIER: US 5959075 A
TITLE: Testis-specific insulin homolog polypeptides

ABPL:
The present invention provides testis-specific insulin homolog polypeptides and polynucleotides encoding the polypeptides, as well as related compositions and methods are disclosed. The polypeptides and polynucleotides may be used within methods for enhancing viability of cryopreserved sperm, for enhancing sperm motility, to enhance fertilization in methods of assisted reproduction, as contraceptives and other related uses.

BSPR:
Spermatogenesis is the process by which a germ cell proceeds through multiple stages of differentiation, and culminates in the formation of a terminally differentiated cell with a unique function. Hematopoiesis can be used as a paradigm for understanding spermatogenesis, and while there are striking parallels between what is known about hematopoiesis and spermatogenesis, the maturation of spermatogonia (germ cells) is less clearly understood than the maturation of hematopoietic stem cells. Particularly deficient is an understanding of factors that regulate the maturation process in spermatogenesis. Recent evidence suggests that some cytokines involved in the progression of stem cells of the hematopoietic lineage to fully differentiated cells are also involved in sperm cell maturation. In a fashion similar to cytokine action in hematopoiesis, these cytokines are thought to act at specific stages in the germ cell's maturation. For example, stem cell factor (also known as Steel factor and c-kit ligand) mRNA is expressed in spermatogonia (Manova et al., Development 110: 1057-1066, 1990), and administration of a monoclonal antibody to stem cell factor to adult or prepubertal mice causes depletion of differentiating spermatogonia but has no effect on the non-differentiating spermatogonia, or spermatocytes (Yoshinaga et al., Development 113: 689-699, 1991). Other cytokines that have been associated with spermatogenesis include IL-1, IL-6 and .beta.-TGF (Sharp, Regulation of Spermatogenesis, in Knobil and Neil (ed.), Physiol. Reproduction, (2nd ed.), Raven, N.Y., 1994).

BSPR:
Within anther aspect, the invention provides a method of enhancing fertilization during assisted reproduction wherein a Zins2 testis-specific insulin homolog polypeptide selected from the group consisting of:

BSPR:
(a) polypeptides comprising a sequence of amino acids encoded by the nucleotide sequence as shown in SEQ ID NO: 1 or SEQ ID NO:12; (b) species homologs of (a); (c) allelic variants of (a) and (b); and (d) Zins2 testis-specific insulin homolog polypeptides which are at least 85% identical to (a), (b) or (c) is combined with sperm, an egg, an egg-sperm mixture prior to fertilization of the egg. Within one embodiment is provided a method of enhancing fertilization wherein the assisted reproduction is artificial insemination. Within a related embodiment is provided a method of enhancing fertilization wherein the assisted reproduction is in vitro fertilization.

DEPR:
Paracrine factors that cross the cellular barrier and enter the sperm cell microenvironment include molecules secreted from Leydig cells. Leydig cells are located in the interstitial space found between the seminiferous tubules, and produce several factors believed to play an important role in spermatogenic cell maturation process, such as testosterone, Leydig factor, IGF-1, inhibin and activin. The expression of these, and other factors, may be specific to a defined stage in the spermatogenic cycle. The sperm is then transported to the epididymus, where sperm motility and fertilization capacity are increased. The sperm is stored in the tail of the epididymus until released.

DEPR:
Other activities, for example, chemotaxic activity that may be associated with proteins of the present invention can be analyzed. For example, late stage factors in spermatogenesis may be involved in egg-sperm interactions and sperm motility. Activities, such as enhancing viability of cryopreserved sperm, stimulating the acrosome reaction, enhancing sperm motility and enhancing egg-sperm interactions may be associated with the proteins of the present invention. Assays evaluating such activities are known (Rosenberger, J. Androl. 11: 89-96, 1990; Fuchs, Zentralbl Gynakol 11: 117-120, 1993; Neurwinger et al., Andrologia 22: 335-9, 1990; Harris et al., Human Reprod. 3: 856-60, 1988; and Jockenhovel, Andrologia 22: 171-178, 1990; Lessing et al., Fertil. Steril. 44: 406-9 (1985); Zaneveld, In Male Infertility Chapter 11, Comhaire Ed., Chapman & Hall, London 1996; all incorporated herein by reference). These activities are expected to result in enhanced fertility and successful reproduction.

DEPR:
Accordingly, proteins of the present invention may have applications in enhancing fertilization during assisted reproduction in humans and in animals. Such assisted reproduction methods are known in the art and include artificial insemination, in vitro fertilization, embryo transfer and gamete intrafallopian transfer. Such methods are useful for assisting men and women who may have physiological or metabolic disorders that prevent natural conception. They may be used to enable women who wish to bear children but do not wish to, or are unable to conceive naturally. Such methods are also used in animal breeding programs, such as for livestock breeding and could be used as

methods for the creation of transgenic animals. Proteins of the present invention can be combined with sperm, an egg or an egg-sperm mixture prior to fertilization of the egg. In some species, sperm capacitate spontaneously during in vitro fertilization procedures, but normally sperm capacitate over an extended period of time both in vivo and in vitro. It is advantageous to increase sperm activation during such procedures to enhance the likelihood of successful fertilization. The washed sperm or sperm removed from the seminal plasma used in such assisted reproduction methods has been shown to have altered reproductive functions, in particular, reduced motility and zona interaction. To enhance fertilization during assisted reproduction methods sperm is capacitated using exogenously added compounds. Suspension of the sperm in seminal plasma from normal subjects or in a "capacitation media" containing a cocktail of compounds known to activate sperm, such as caffeine, dibutyl cyclic adenosine monophosphate (dbcAMP) or theophylline, have resulted in improved reproductive function of the sperm, in particular, sperm motility and zonae penetration (Park et al., Am. J. Obstet. Gynecol. 158: 974-9, 1988; Vandevoort et al., Mol. Repro. Develop. 37: 299-304, 1993; Vandevoort and Overstreet, J. Androl. 16: 327-33, 1995). The presence of immunoreactive relaxin in vivo and in association with cryopreserved semen, was shown to significantly increase sperm motility (Juang et al., Anim. Reprod. Sci. 20: 21-9, 1989; Juang et al., Anim. Reprod. Sci. 22: 47-53, 1990). Porcine relaxin stimulated sperm motility in cryopreserved human sperm (Colon et al., Fertil. Steril. 46: 1133-39, 1986; Lessing et al., Fertil. Steril. 44: 406-9, 1985) and preserved ability of washed human sperm to penetrate cervical mucus in vitro (Brenner et al., Fertil. Steril. 42: 92-6, 1984, all incorporated herein by reference). Polypeptides of the present invention can used in such methods to enhance viability of cryopreserved sperm, enhance sperm motility and enhance fertilization, particularly in association with methods of assisted reproduction.

DEPR:
In cases where pregnancy is not desired, Zins2 proteins or protein fragments may function as germ-cell-specific antigens for use as components in "immunocontraceptive" or "anti-fertility" vaccines to induce formation of antibodies and/or cell mediated immunity to selectively inhibit a process, or processes, critical to successful reproduction in humans and animals. The use of sperm and testis antigens in the development of an immunocontraceptive have been described (O'Hern et al., Biol Reprod. 52: 311-39, 1995; Diekman and Herr, Am. J. Reprod. Immunol. 37: 111-17, 1997; Zhu and Naz, Proc. Natl. Acad. Sci. USA 94: 4704-9,1997, all of which are incorporated herein by reference). A vaccine based on human chorionic gonadotrophin (HOG) linked to a diphtheria or tetanus carrier is currently in clinical trials (Talwar et al., Proc. Natl. Acad. Sci. USA 91: 8532-36, 1994, incorporated herein by reference). A single injection resulted in production of high titer antibodies that persisted for nearly a year in rabbits (Stevens, Am. J. Reprod. Immunol. 29: 176-88, 1993, incorporated herein by reference). Such methods of immunocontraception using vaccines would include a Zins2 testes-specific insulin homolog protein or fragment

thereof. The Zins2 protein or fragments can be conjugated to a carrier protein or peptide, such as tetanus or diphtheria toxoid. An adjuvant, as described above, can be included and the protein or fragment can be noncovalently associated with other molecules to enhance intrinsic immunoreactivity. Methods for administration and methods for determining the number of administrations are known in the art. Such a method might include a number of primary injections over several weeks followed by booster injections as needed to maintain a suitable antibody titer.

DEPR:
Testis tissue was prepared for in situ hybridization using techniques known in the art. See, for example, Simmons et al., J. of Histotechnology 12: 169-181, 1989; and Sylvester et al., Biol. of Reproduction 45: 195-207, 1991.

ORPL:
Bagnell et al., Journal of Reproduction and Fertility Supplement 48: 127-138, 1993.

ORPL:
Juang et al., Animal Reproduction Science 20: 21-29, 1989.

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L8: Entry 6 of 21 File: USPT Feb 10, 1998

DOCUMENT-IDENTIFIER: US 5716810 A
TITLE: Nucleic acid encoding the mature .beta..sub.B chain of inhibin and method for synthesizing polypeptides using such nucleic acid

DEPR:
Immunogenic conjugates of prodomain polypeptides, inhibin and activin are readily synthesized in recombinant cell culture as fusions with immunogenic polypeptides, e.g. beta-lactamase or viral antigens such as the herpes gD protein, or by preparation of the polypeptides in unfused form (by recombinant or in vitro synthetic methods) followed by covalent cross-linking to an inmunogenic polypeptide such as keyhole limpet hemocyanin or STI using a divalent cross-linking agent. The immunogenic polypeptides are formulated with a vaccine adjuvant, e.g. alum or Freunds. Methods for preparing proteins in adjuvants and for cross-linking are well-known per se and would be employed by one skilled in the art, as are methods for vaccinating animals. The immunogenic conjugates are useful in preparing antibodies to the prodomain region for use in monitoring inhibin manufacture or for in vivo vaccination with the objective of raising antibodies capable of modulating animal physiology in reproductive cycles and fertility. Typically, the prodomain or its immunogen is administered in varied doses to fertile laboratory animals or swine and the reproductive cycles and fertility of the animals monitored, together with assays of serum levels of anti-immunogen or prodomain by routine competitive or sandwich immunoassay.

DEPR:
The inhibin a chain is expressed in recombinant cell culture with or without either of the .beta.-chain molecules. Similarly, host cells are transformed with DNA encoding either or both of the mature .beta.-chains. Based on analogy to TGF-.beta., the mature .beta.-chains are capable of forming homodimers or .beta..sub.A /.beta..sub.B heterodimers upon expression in recombinant culture. These structures are not inhibin and will be referred to herein as .beta.-chain dimers or activin. These are useful in the preparation of active inhibin, serving as sources of the .beta.-chain, or are used as gel electrophoresis standards to detect the diversion into .beta.-chain dimers of .beta.-chains synthesized in .alpha. and .beta. chain cotransformants. As will be seen in Example 4, this is not hypothetical problem. Of course, the dimers also are useful in modulating reproduction as noted above.

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L1: Entry 15 of 35 File: USPT Dec 2, 1997

DOCUMENT-IDENTIFIER: US 5693496 A
TITLE: DNA encoding the mouse and human PH30 beta chain protein

DEPR:
In the Examples which follow, Applicants describe the cloning and characterization of the mouse and human PH30 beta chain genes. The mouse and human PH30 beta chain genes were isolated using a cDNA encoding the guinea pig PH30 beta chain gene. The instant invention provides specific sequence information to permit targeted intervention in controlling fertility through anti PH30 directed immune responses inhibition of sperm-egg binding and triggering of post binding signaling and effective events. These sequences permit the generation of reagents for the isolation of oocyte proteins involved in sperm-egg interaction.

DEPR:
The cloning and characterization of human PH30 beta permits novel approaches for using PH30 as a target to control human fertility. PH30 beta protein or peptides can be used directly as an antigen to elicit an immune response directed to the whole or a relevant part of the PH30 beta chain protein. Testing of these approaches requires availability of sufficient quantities of PH30 beta protein. The cloning and sequencing of the mouse and human PH30 beta chain provides information necessary to recombinantly express all or part of the PH30 beta protein. These expressed proteins are used with or without adjuvant to immunize women or female mice. The elicited humoral immune responses are monitored by assays that use PH30 beta as antigen. Secreted antibodies in the female reproductive system will bind to the sperm head and disrupt fertilization. The availability of the recombinant mouse PH30 beta protein permits establishment of an animal model system for testing efficacy, reversibility and safety of specific methods of controlling fertility based on PH30.

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L1: Entry 11 of 35 File: USPT Jul 7, 1998

DOCUMENT-IDENTIFIER: US 5776465 A
TITLE: Recombinant mycobacterial vaccines

BSPR:
The recombinant mycobacteria can also be used as a vehicle for expression of cytokines, immunopotentiators, enzymes, pharmacologic agents and antitumor agents; expression of a polypeptide or a protein useful in producing an anti-fertility vaccine vehicle; or expression of stress proteins, which can be administered to evoke an immune response or to induce tolerance in an autoimmune disease (e.g., rheumatoid arthritis). Recombinant mycobacteria can, for example, express protein(s) or polypeptide(s) which are growth inhibitors or are cytocidal for tumor cells (e.g., interferon .alpha., .beta. or interleukins 1-7, tumor necrosis factor (TNF) .alpha. or .beta.) and, thus, provide the basis for a new strategy for treating certain human cancers (e.g., bladder cancer, melanomas). Pathogens of interest include any virus, retrovirus, microorganism, or other organism or substance (e.g, a toxin or toxoid) which causes disease. The present invention also relates to methods of vaccinating a host with the recombinant mycobacterium to elicit protective immunity in the host. The recombinant vaccine can be used to produce humoral antibody immunity, cellular immunity (including helper and cytotoxic immunity) and/or mucosal or secretory immunity. In addition, the present invention relates to use of the polypeptide(s) or protein(s) such as antigens or cytokines, expressed by the recombinant cultivable mycobacterium as vaccines or as diagnostic reagents.